

To Evaluate the Complications of TRUS guided Prostate Biopsy



A dissertation submitted to The Dr. M.G.R. Medical University, Tamilnadu, in partial
fulfillment of the requirements for M.Ch. Branch-IV (Genitourinary surgery)
examination to be held in August 2014

DEPARTMENT OF UROLOGY
CHRISTIAN MEDICAL COLLEGE, VELLORE

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled “**To Evaluate the complications of TRUS guided prostate biopsy**” done towards fulfilment of the requirements of the **Tamil Nadu Dr. M.G.R. Medical University, Chennai for the M.Ch (Branch– IV) (Urology)** exams to be conducted in August 2014, is a bonafide work of the candidate **Dr. Feroz Mohd Khan**, Senior Post graduate student in the Department of Urology, Christian Medical College, Vellore under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

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Sub: Fluid Research grant project:
To evaluate the complications of TRUS guided prostate biopsy.
Dr. Feroz Mohd Khan, Senior Registrar, Department of Urology,
Dr. Nithi S Keer, Dr. Nirmal T. J., Urology.

Ref: IRB Mtn No. 8452 dated 10.09.2013

Dear Dr. Feroz Mohd Khan,

The Institutional Review Board (Blue Research & Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "To evaluate the complications of TRUS guided prostate biopsy" on September 10, 2013.

The Committees reviewed the following documents:

1. Format for IRB application
2. Informed Consent form in English, Tamil & Bengali.
3. CV's of Dr. Feroz Mohd Khan, Nithi S Keer & Nirmal T. J.
4. No of documents 1-3

The following Institutional Review Board (Blue Research & Ethics Committee) members were present at the meeting held on September 10, 2013 in the CRST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any adverse events occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Policies.html in the CMC Intranet and in the CMC website link address: <http://www.cmcvellore.edu/static/research/index.html>.

Yours sincerely

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ANNEXURE

- Patient Performa
- Patient information
- Consent form

ABBREVIATIONS

TRUS – Trans rectal Ultrasound

PSA – Prostate Specific Antigen

UTI – Urinary tract Infection

VAS – Visual Analogue Scale

LUTS - Lower urinary tract symptoms

PPNB – Peri prostatic nerve block

ASAP – Atypical small acinar proliferation

HGPIN – High grade prostatic intra epithelial neoplasia

LMWH – Low molecular weight heparin

FORMAT

TITLE OF THE ABSTRACT: To evaluate the Complications of TRUS guided Prostate Biopsy

DEPARTMENT : UROLOGY

NAME OF THE CANDIDATE : DR FERAZ MOHD KHAN

DEGREE AND SUBJECT : MCh UROLOGY

NAME OF THE GUIDE : DR NITIN SUHAKAR KEKRE

AIM / OBJECTIVES: Describe the objectives of your study (maximum 30 words)

The aim of the study was to assess prospectively, the complications following TRUS guided prostate biopsy. The primary objective of the study was to assess urosepsis requiring hospitalisation. The secondary objective was to assess the incidence of other complications following TRUS guided prostate biopsy. These include; fever, hematuria, hematochezia, urinary retention and pain or discomfort.

MATERIAL AND METHODS: Explain the clinical and statistical methods used (maximum 100 words)

All consecutive patients under evaluation of suspected carcinoma prostate were included in the study. All patients underwent detailed history and physical examination. Standard 12- Core prostate biopsy done. Inclusion Criteria: Raised prostate specific antigen (PSA >4.0 ng/ml), abnormal digital rectal examination (DRE) or outside biopsy report suggestive of prostate cancer but no slides/blocks available for review. Exclusion Criteria: Patients refused to give consent, patients started on prophylactic antibiotics two days prior to biopsy.

RESULTS: Summarise the findings and conclusions of your study (maximum 90 words)

A total of 89 patients underwent TRUS guided prostate biopsy. Fourteen patients were excluded from the study as they received oral prophylaxis before prostate biopsy

regardless of their urine culture report. The remaining seventy five patients were included in the study. The mean age of patients was 60.69 years. Diabetes and hypertension were the most common associated co-morbid illnesses. Most common presentation was lower urinary tract symptoms. Only five patients developed low grade fever. One patient developed urosepsis and septic shock after prostate biopsy and was hospitalised. Subgroup analysis showed that patients with positive urine cultures had more infection as compared to the other group where urine culture was either sterile or contaminants. Diabetic patients had more incidence of infection compared to non-diabetics. Ten patients were on catheter prior to prostate biopsy. There was no infection noted in this group following biopsy.

CONCLUSIONS:

Trans rectal ultrasound guided prostate needle biopsy is safe for diagnosing prostate cancer. The most common complication was hematuria in 26.4% of cases, followed by low grade fever. Incidence of sepsis requiring hospitalisation was very low in our study. Increased incidence of infection in patients with positive urine culture suggests that treatment of infection and documentation of negative urine culture before biopsy may be wiser. Positive 7pre-biopsy urine culture and diabetes mellitus are risk factors which should be looked into before planning prostate biopsy.

Keywords: Trans rectal ultrasound; Lower urinary tract symptoms; sepsis, prostate specific antigen.

Introduction

The most common non-cutaneous cancer in United States is prostate cancer, an approximate 241,000 cases diagnosed in 2012. And also, the second most common cause of cancer-related death (1). The recommended methods for screening of prostate cancer are prostate specific antigen (PSA) test and rectal examination. But prostate needle biopsy is necessary to make the diagnosis. Prostate biopsies were originally done with either digitally guided or trans-perineal biopsy trucut. But with the development of trans rectal ultrasound, all trucut biopsies have been replaced by trans rectal ultrasound (TRUS)-guided prostate biopsy (2).

Majority of the prostate biopsy related complications are mild and self-limited but sometimes it could be severe and life threatening. Infection, bleeding, and urinary retention are the most common complications after prostate biopsy. Among Infectious complications, mild fever, febrile UTI, and sepsis are common (3–6). Recently, there is an increase in hospitalisation rate due to infectious complication following prostate biopsy (7). Multiple factors could be responsible for recent trends. Bacterial resistance to fluoroquinolones and the lack of standard regimen for antimicrobial prophylaxis before prostate biopsy apparently the most common factors (8–11).

This is a prospective study, designed to evaluate the complications of TRUS guided prostate biopsy.

Aims and Objectives

AIMS:

The aim of the study was to assess prospectively, the complications following trans rectal ultrasound (TRUS) guided prostate biopsy.

OBJECTIVES:

Primary objective of the study was to assess urosepsis requiring hospitalisation.

Secondary objective was to assess the occurrence of other complications following biopsy of prostate. These include-

- Fever
- Hematuria
- Hematochezia
- Urinary retention
- Pain or discomfort

Review of Literature

Historical Perspective:

Prostate biopsy was first described by Ferguson in 1930. He obtained cancer cells by aspirating prostate tissue with 18G needle, trans-perineally (12). The first trans rectal core needle prostate biopsy was performed by Astraldi in 1937 (13). There were various instruments developed and modifications occurred since then for core needle biopsy. All biopsies were done using finger guidance for palpable abnormality of prostate, either trans perineal or trans rectal route.

Wild and Reid in 1955, first reported use of trans rectal ultrasound (TRUS) of prostate. It was popularised by Watanabe et al. in 1970 (14,15). TRUS guided prostate biopsy was started in late 1980s using 18 Gauge needle on a spring device (Biopty Gun). Since then it has become a standard procedure. The “sextant biopsy” model was proposed by Hodge in 1989 (16). Sextant biopsy was standard method for prostate biopsy until Stamey in 1995, suggested taking samples from more lateral parts of the prostate to include peripheral zones. Studies of radical prostatectomy specimen section analysis had shown that prostate cancer most commonly arises from peripheral zones. Therefore laterally directed biopsies were advice to increase the yield of cancer detection as well as reduce the missing out cancer foci (17). Thereafter, technological advancement has improved the TRUS and its role in prostate cancer detection. Recent advancement in prostate imaging includes Colour Doppler, MR spectroscopy, MRI/TRUS fusion analysis and prostate Elastography. They are particularly

useful in cases where 1st biopsy came as negative but clinical suspicion for prostate carcinoma is high.

Epidemiology of carcinoma prostate:

Incidence of prostate cancer is commonest non skin cancer in U.S. population. The lifetime risk of disease is estimated to be approximately 16%, with a 2.5% risk of death. Among U.S. population, African-Americans have the highest incidence of carcinoma prostate. Worldwide, it is the 5th most common cancer and the 2nd second most common among men. Overall, incidence of carcinoma prostate was about 12%, 19% in developed countries and about 5% in the developing countries. There is a wide variation of incidence among countries and ethnicity. Asia has lowest incidence rates and highest among North America and Scandinavian population (1,18). Introduction of PSA has led to much increase in incidence of prostate cancer. Similar to prostate cancer incidence, there is wide variation in mortality among countries. Highest rate of mortality in African countries southeast China, Asia and North Africa has lowest mortality (18). The CONCORD study analysed cancer survival in different countries and reported different survival rates for colorectal, breast and prostate cancer. There was large variation in 5-year survival rates; it was highest in the Canada, Australia, and United States and to lowest in Algeria, Poland and Denmark. The accuracy of cancer registries, access to health care and quality of health care as well as PSA screening affect prostate cancer reporting (19).

In recent period, there have been efforts to diagnose prostate cancer at earlier stage. This has resulted in diagnosing increased number of clinically insignificant prostate cancer,

described as small-volume, lower-grade prostate cancer. The 10-yr survival rate was similar to general population (20,21).

Despite screening programme to detect early prostate cancer, a large number of significant prostate cancers are still under diagnosed. Under-diagnosis was defined as inability to diagnose high grade, high-risk, locally advanced or surgical margins positive, if resected, prostate cancer (22).

Over-detection was defined as detection of small volume prostate cancer, localised with Gleason score ≤ 4 or 5. Studies showed that about 1–7% of patients were over diagnosed and the resulting into consequent overtreatment. Over-diagnosis of prostate cancer is a major concerns in prostate oncology (23).

Role of Prostate Biopsy:

Initially prostate biopsy was used to diagnose prostate cancer. Now it has evolved from not only to detect cancer but to assist in clinical management of patient. Prostate biopsy plays an important role in active surveillance (AS) programme. Therefore it should be reproducible. It has an important role in standardised staging and grading of prostate cancer (20).

Historically, sextant biopsy was the standard to diagnose prostate cancer. Studies showed that there was increased number of missing clinically significant prostate cancers due to sampling error while doing sextant biopsy. This has resulted to the introduction of extended-core prostate biopsy strategies (24–27). One study has assessed the role of

extended biopsy in Gleason stage up gradation. It included 301 patients with low-risk prostate, an extended (≥ 10 -core) prostate biopsy was done. 18 cores of biopsy were taken in majority of patients. The up gradation was reported in 31.9% patients (28).

To detect missed cancer and to assess the tumor volume as well as prognosis, extended or saturation prostate biopsies were advised (29).

Risk stratification of prostate cancer: (30)

There are three risk categories described for prostate cancer;

Low risk group: PSA < 10, Gleason score ≤ 6 and stage T1 or T2a.

Intermediate risk group: PSA 10 - 20, or Gleason score = 7 or stage T2b or T2c.

High risk group: PSA > 20, or Gleason score ≥ 8 or stage T3, or two or more intermediate risk factors.

Watanabe was the first to describe trans rectal ultrasonography (TRUS) of the prostate in 1968, later with technological advancement of ultrasound and use of trans rectal ultrasound for prostate biopsy, it was included in routine clinical use (16). Increased numbers of patients are undergoing TRUS guided prostate biopsy annually in the United. Prostate cancer prevalence is high similarly large number of patients undergoing trans rectal prostate biopsy under ultrasound guidance now a days.

Ultrasonography of the Prostate:

The prostate gland is located anterior to rectum between the bladder neck and the urogenital diaphragm.

Prostate gland is divided into following zones-

- Anterior fibro muscular stroma (AFS)
- Central zone (CZ)
- Transition zone (TZ)
- Peripheral zone (PZ)
- Periurethral zone

These zones cannot be differentiated on trans rectal ultrasonography (TRUS). Central and peripheral zones of the prostate are located posteriorly and appear homogenous on TRUS. Most of the adenocarcinoma prostate arises from these regions. Multiple, small and diffuse calcifications of the prostate are a normal ultrasonographic finding. It is an age related and not a pathological. Prostatic calculi are symptomatic if large, needs further evaluation and treatment.

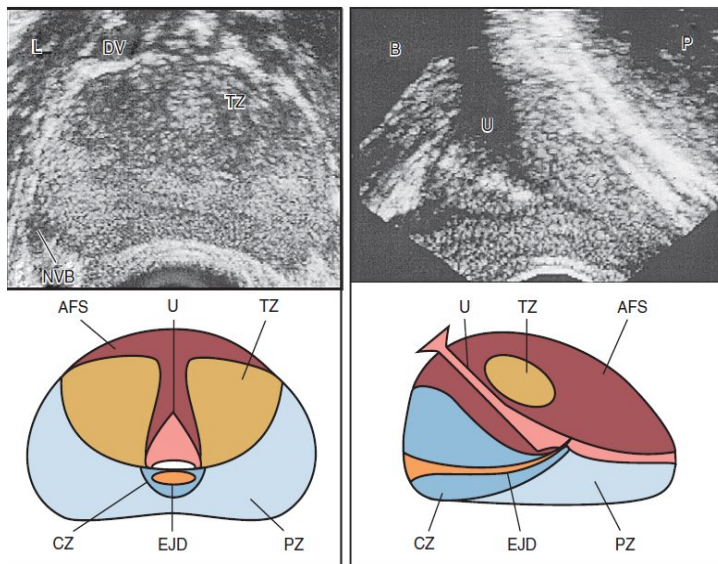


Figure 1
Normal Trans rectal ultrasound image.
A, Transverse view. B, Sagittal view

AFS, anterior fibro muscular stroma;
CZ, central zone; DV, dorsal vein
complex; EJD, ejaculatory ducts;
TZ, transition zone; U, urethra.

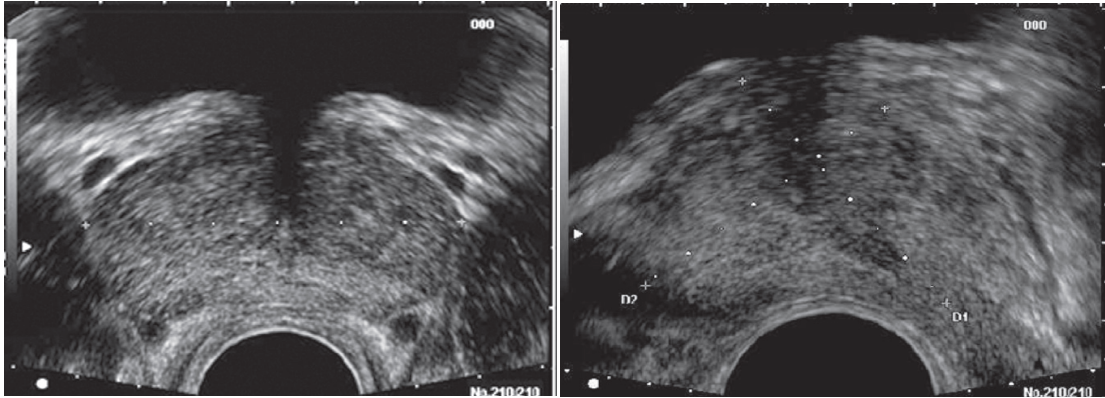


Figure 2
Trans rectal ultrasound image of the prostate.
A, In the transverse
B, Midline sagittal view.

Gray-scale trans rectal ultrasonography (TRUS):

Currently, TRUS is the most common imaging for prostate evaluation. The most common use of TRUS is for prostate cancer detection, there is other indications also esp. Infertility where it can be useful. There are two types of endorectal probes, side-fire and end-fire models with 6 to 10 MHz frequencies. The biplane probes give simultaneous transverse as well as sagittal views. The resolution of images increases with increase in frequency of ultrasound probe. High frequency probes have small focal length and image is very close to the transducer. The 7-MHz transducer results in high-resolution image and is best for peripheral zone of prostate. Lower frequency probes have large focal length but the resolution of images will be low. They are accurate of volume measurements.

Techniques:

Prostate should be evaluated in both transverse as well as sagittal planes. Prostate volume is calculated. Hypo-echoic lesions are looked in central and peripheral zones.

Patient positioning during TRUS:

Left lateral position is the most preferred position for prostate biopsy.

Prostate Volume Calculations:

Various formulas are described for calculation of prostate volume. Prostate measurements are taken in three dimensions, axial plane, transverse and antero-posterior, to calculate the volume. Most commonly used formula is -

- Prolate spheroid ($\pi/6 \times \text{transverse diameter}^2 \times \text{antero-posterior diameter}$).

Hypo-echoic lesions within peripheral zones should be identified and biopsied. Majority of suspected lesions for prostate cancer are hypo-echoic lesions. About 39% of malignancies are iso-echoic and ~1% of tumors are hyper-echoic on TRUS. Although hypo-echoic lesions are most commonly turn out to be prostate cancer, other disease processes like granulomatous prostatitis, prostatic infarct and lymphoma can also produce hypo-echoic lesions. About 17% to 57% of cases, a hypo-echoic lesion is malignant, required to biopsy these lesions. Any contour abnormalities along the surface of the gland are suspected to be prostate cancer. Extra capsular extension of prostate cancer is noted by loss of bright white peri prostatic fat (31).

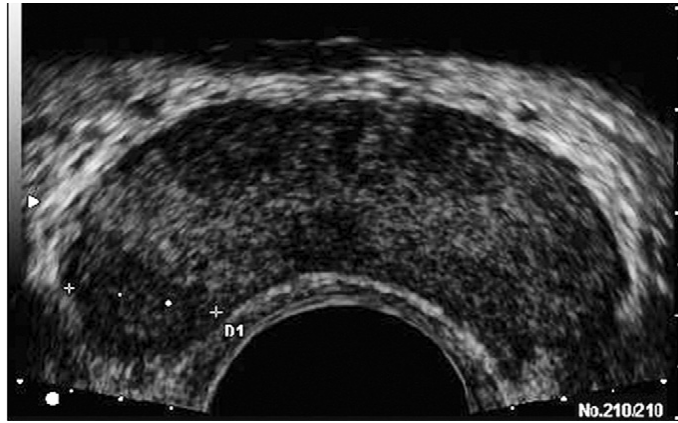


Figure 3: Hypo-echoic lesion noted on the right lateral aspect of prostate

Prostate biopsy under image guidance:

Prostate gland imaging improves cancer detection by precisely visualising and characterising the lesion as well as to guide the accurate and targeted biopsy. Currently, with the help of newer imaging modalities such as MRI and contrast enhanced TRUS, a higher number of image-targeted cancers in suspicious lesions have been found (32–34). These studies have shown that targeted biopsies detect cancer of high grade and tumor volume than that of conventional TRUS biopsy. Therefore targeted biopsy may be helpful in prostate cancer grading, prognosis and deciding treatment. Recent studies had introduced modern imaging, such as elastography. A prospective randomised study showed sensitivity and specificity of real-time elastography as 61% and 68% respectively as compared to grey-scale ultrasound which showed sensitivity and specificity of 15% and 92% respectively (35).

Routine prostate biopsy may be called as image-blinded prostate biopsy. Tumor lesions identified on image will result in better yield of malignant tissue than the image-blinded

procedure. Image localisation of cancer provides precise identification of the cancer, which would result in better lesion-targeted management. A systematic review on targeted biopsy using image-guided prostate biopsy and MRI localised lesions had shown that cancer was detected in 30% of MRI targeted cores versus 7% of systematic cores (36).

Another newer modality of prostate is MR/TRUS image fusion (37). However, Utility of MRI/TRUS fusion imaging needs to be validated as the prostate is a deformable organ changes its shape during TRUS but it remains the same on MRI (20).

Role of MRI/MR spectroscopy:

Recently, the role of MR spectroscopy and targeted biopsy was assessed. The high diagnostic accuracy of magnetic resonance spectroscopic imaging and dynamic contrast-enhanced imaging magnetic resonance (DCEMR) in the management of prostate cancer was evaluated in one study. MRS detects metabolic activity of tissues and can differentiate normal from cancerous tissue based on ratios of creatine, choline and citrate production and consumption (38). Cancerous tissue contains less citrate level and higher concentrations of choline and creatine when compared with benign prostatic hypertrophy or normal prostatic tissue. A randomised controlled trial, recently evaluated the role of MRS and dynamic contrast enhanced MR (DCEMR) imaging in cases of prior negative biopsy but high suspicion of prostate cancer. The patients with a prior negative prostate biopsy and persistently elevated PSA levels, a combination of a standard 10-core biopsy scheme with an oversampling strategy in sites targeted by combined MRSI/DCEMR indications resulted in significantly higher cancer detection rates. At the second biopsy, a prostate cancer detection rate was significantly high among those where MRS/DCEMR technique were utilised (P =

0.01). The prostate cancer detected with the help of MRS/DCEMR were high grade (Gleason score ≥ 7 (4+3) 61.6%) (39).

Prostate Biopsy Technique:

18 Gauge needle loaded on a spring action device is used for prostate biopsy. When trigger button of device is pushed, the inner needle advances 23 mm followed by outer hollow core needle. The prostate tissue is caught between inner needle and outer sheath and therefore disengaged from the prostate gland. The device is design to obtain 15 mm to 17 mm length of the tissue during biopsy.

Techniques of Extended Core Biopsy:

The sextant biopsy had a low yield of cancer detection therefore sampling of more tissue from laterally focused cores are introduced. Various studies have shown improved detection rate of cancer by laterally directed biopsy cores in addition to the standard systematic sextant technique. Extended core biopsy includes 8 to 13 cores (24,40,41). 6 cores biopsy is not adequate for prostate cancer detection.

Transition zone as well as seminal vesicles is not routinely sampled because of low cancer detection rate at initial biopsy. Transition zone biopsy may help in case of large gland (more than 50 ml). It increases additional 15% chances of cancer detection.

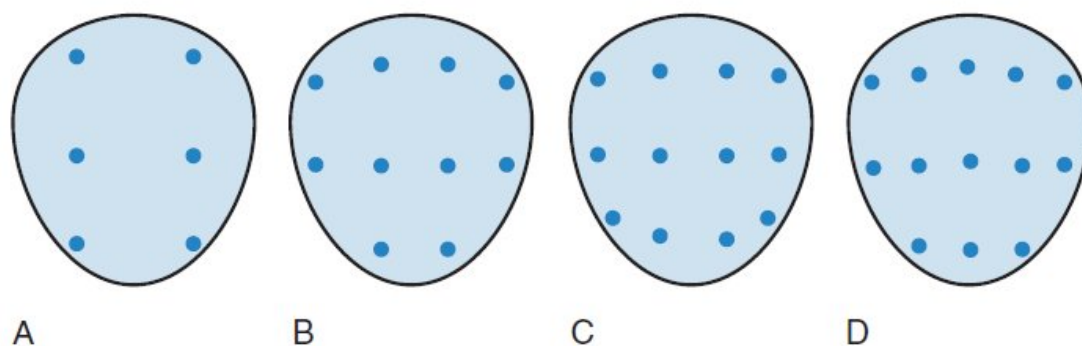


Figure 4

A, Sextant biopsy B, 10-core biopsy C, 12-core biopsy

D, 13-core or "5-region biopsy"

Trans rectal ultrasound guided prostate needle biopsy is the gold standard for diagnosing prostate cancer. PSA based screening programs has resulted in detection of early prostate cancer. There is a significant increase incidence of organ confined disease and potentially curable due to PSA screening (42). Most accepted PSA threshold above which biopsy advised is >4.0 ng/ml, although optimal PSA threshold is not yet defined in asymptomatic men. As the PSA threshold was lowered to >2.5 ng/ml, it has resulted in increased detection of organ confined prostate cancer at the time of radical prostatectomy.

This observation has led to recommendation of prostate biopsy in younger men (below 60 years if PSA rises above 2.5ng/ml (43). There is no PSA level that can exclude prostate cancer in age range as shown in Prostate Cancer Prevention (PCPT) Trial. Thompson and colleague in their data showed that men with PSA less than 4.0 ng/ml, large numbers of patients were diagnosed as prostate cancer. Prostate cancer was diagnosed in 15% of patient with PSA level < 4.0 , and there will be 15% of patient having a Gleason score of ≥ 7 (22).

To reduce the chances of under-diagnosis of high risk disease, prostate biopsy was extensively performed as well as PSA threshold for performing biopsy was also reduced in the last decade. This has resulted to increased number of “insignificant cancer” being diagnosed. Similarly, there is an increased number of biopsy cores to diagnosed prostate cancer.

Urinary tract infection (UTI) or prostatitis may cause false elevation of PSA. Most of the cases, PSA value ranges between 2.5–10.0. Guidelines recommend repeating such abnormal PSA value before deciding upon performing prostate biopsy (20).

Number of prostate biopsy cores:

Increased numbers of cores and proper localisation of these cores were considered optimal to sample entire prostate. Haas et al. did biopsy on prostates of 164 autopsy patients. 18-core biopsy was performed in all patients. Analysis showed that 12-core specimen detected most of cancers which is clinically significant with 80% sensitivity (44). It was found that cancer detection was related more to location of samples rather number of biopsy cores and samples containing lateral and apical cores were representing the peripheral zone (PZ) tissue where prostate cancer mostly occurs.

Initial biopsy:

Currently the 12-core biopsy is widely accepted method of biopsy. Some studies did show that taking biopsy cores from apical region on each side improves the yield of detecting prostate cancer. Cancer is missed mostly at the apical location during initial biopsy (45). Controversy exists regarding number of biopsy cores and age of the patient as well as

volume of prostate. Extended biopsy has a significant superiority of cancer detection rate when compared with sextant biopsy (46). Studies have shown that extended biopsy cores >12–14 as initial prostate biopsy scheme has no advantage over standard 12-core biopsy (47,48).

Repeat biopsy:

Indications:

- Inadequate prostatic tissue to diagnose or exclude prostate cancer.
- Previous negative biopsy but persistent clinical or biochemical suspicion for carcinoma prostate (e.g. abnormal DRE, persistently raised or rising PSA).
- Previous biopsy of multifocal High Grade PIN and/or Previous Suspicious Appearances (ASAP)

Systematic prostate biopsy has the potential to miss small volume prostate cancer in some patients. Therefore these patients undergo repeat biopsy. About 30% to 50% of patients detected to have cancer on repeat biopsy, mostly with extended biopsy scheme (20).

Scattoni et al. proposed a model for repeat prostate biopsy considering the clinical characteristics of the patients. Patients with ASAP, a 14-core biopsy without TZ sampling were done. A 14-core biopsy with four TZ cores if there is no ASAP but %free PSA was $\leq 10\%$. If there is no ASAP and %free PSA $> 10\%$, a 20-core biopsy including four TZ cores was found to be useful (49).

Ideally, samples should be located at different sites after negative biopsy to identify tumours which were not sampled in the previous biopsy. In case of multifocal HGPIN or ASAP, repeat biopsy to an adjacent sites should be sampled. In about half of the cases of ASAP, cancer is found in the same

location. There is a risk of carcinoma in the entire gland in case of HGPIN (50,51). The natural history of atypical small acinar proliferation (ASAP) is not well defined as compared to HGPIN, if ASAP is seen in the biopsy, there is a significant chance of diagnosing prostate cancer on repeat biopsy. Current recommendations are to repeat biopsy within 3 to 6 months in case of ASAP or HGPIN on initial biopsy. The most common areas missed during initial biopsy are apices and anterior prostate.

Saturation Biopsy:

Saturation biopsy has been recommended by some investigators to maximise the cancer detection rate in patients where the clinical criteria put them at high risk for prostate cancer despite a previous benign biopsy. It has been performed with peri prostatic nerve block, under sedation or under general or spinal anaesthesia (26,52). The office-based trans rectal saturation biopsy technique with biopsy cores of ≥ 20 has increased the prostate cancer diagnosis by 30%. However, complication rate was similar to that of standard biopsy (53). Cancer detection rate by saturation biopsy protocol is similar to extended core (10-12 Core) biopsy, which is less morbid procedure. Therefore role of saturation biopsy has decreased with time.

When serum PSA level is in the range of 4.0 to 10.0 ng/ml, % free PSA less than 25% helps in 95% chances of detection of prostate cancer and avoids 20% prostate biopsies, and the risk of cancer increased further decline of free PSA (42). Similarly, a PSA velocity >0.75 ng/ml/year has increased suspicion of prostate cancer and suggests biopsy (54). The clinical utility of PSA velocity is controversial in detecting clinically significant prostate cancer.

Before deciding on a repeat prostate biopsy to detect suspected prostate cancer, an elevated PSAD and PSAD-TZ suggests repeat biopsy to diagnosed prostate cancer.

Prostate Biopsy contraindications:(55)

- Significant coagulopathy
- Painful condition
- Immunosuppression
- Acute prostatitis

Prophylactic Antibiotics:

There are various prophylactic antibiotic regimens described. American Urological Association recommends antibiotic prophylaxis before trans rectal prostate biopsy (56). Controversy exists regarding the duration of antibiotics after biopsy. Studies have shown that fluoroquinolone prophylactic regimens, single-dose oral is equally effective than 3-day regimens to prevent infections (56,57).

Rectal Cleansing Enema prior to Biopsy:

Various strategies reducing infectious complications have been explored. One study by Gil-Vernet used povidone-iodine for rectal cleansing prior to prostate biopsy and reported 0.2% incidence of E. coli epididymitis. Another study using the same protocol also showed similar result (58,59). Contrary to these studies, Zaytoun et al. could not find any difference in complications using enema (60). Cochrane review has concluded that risk of bacteraemia was reduced with enema plus antibiotics in comparison to antibiotics only but risk of fever or infection was similar (6).

To reduce the infectious complications, several studies have assessed the role of expanding the antimicrobials, using different techniques for biopsy and rectal swab cultures. Adding ciprofloxacin to amoxicillin-clavulanate resulted decreased of infections(61). Adibi et al. evaluated the addition of gentamicin to trimethoprim-sulfamethoxazole or ciprofloxacin and compared it with the group where gentamicin was not added and noticed decreased rate of hospitalization (62). Another study have reported favourable results with addition of amikacin (63). Ceftriaxone was added to lidocaine during peri-prostatic nerve block in one study, resulted in decreased incidence of sepsis (64). Drawbacks of broad spectrum prophylaxis are increased adverse effects, potential increase in antimicrobial resistance and cost. However, the expenses of hospitalisation increases significantly if admission is required due to post biopsy infection rather using more intensive prophylaxis prior to biopsy and it is more cost effective. There is another concept of targeted prophylaxis under investigation. A culture swab from rectum is taken and is plated on agar. Patients' ciprofloxacin sensitive rectal swab cultures can receive the same as prophylaxis; others to get alternate antibiotics. Positive swab culture from rectum is considered as risk factor for prostate biopsy related infection but it does not always lead to clinical infection. Several prevalence studies have shown that approximately 25% of rectal swab cultures contain fluoroquinolone-resistant organisms but actual clinical infection occurs in a very small number of these patients (11).

There are no randomized control trials to show that targeted prophylaxis decreases the chances infection and expenditure when compared with routine prophylaxis.

There are studies showed that technical modifications had influenced the incidence of infection. Trans perineal approach has been suggested as an alternative technique for prostate biopsy as it bypasses the rectum which is the source of bacterial contamination and subsequent infection. Although it did not result in reduction of infection (65). Size of needle

or cleaning the needle with iodine solution is not associated with infectious risk. There are conflicting reports regarding infectious risk while using same needle in subsequent patients or new needle each time for biopsy. However, adequate reprocessing/disinfection of biopsy probes and needle guide are of paramount importance. General recommendations for assessment of patient prior to prostate biopsy include a complete evaluation including history and examination and risk factor assessment for bacterial resistant and infectious complications (66).

Risk factors for infectious complications:(66)

Patient-related:

- Co morbidities; Diabetes, COPD
- Heart valve
- Benign prostate enlargement
- Recent UTI
- Recent antibiotics usage, particularly fluoroquinolone
- Hospitalisation in the recent past
- Indwelling urethral catheter
- Pre biopsy urine culture positivity

Procedure-related:

- Increase number of biopsy cores
- Repeat biopsy
- Contaminated ultrasound gel

Infection following TRUS biopsy:

Infection following TRUS guided prostate biopsy is a well-established risk, therefore evidence supporting antimicrobial prophylaxis. Regarding use of prophylactic antibiotics, a Cochrane review has reported significant reduction of bacteriuria, bacteraemia, incidence of fever, urinary tract infection (UTI), and rate of hospitalisation (6). American Urological Association recommends routine antimicrobial prophylaxis for TRUS-biopsy. Majority of

centres use prophylactic antibiotic prior to prostate biopsy however, there was a wide variation among studies regarding duration of antimicrobial use, many of these studies did not show significant benefit if used for >24 hours period (67–70).

Incidence of infection and related complications:

Infection rate varied in different studies, with reported rate of hospitalization range from 0–6.3% (71,72). One study on infection have reported, incidence of UTI in about 3.5% patients and 3% required hospitalisation after biopsy. Simsir et al showed similar incidence of septicaemia (73,74). Contrary to them, other studies had shown decreased incidence of sepsis (0.6% to 1.7%) following prostate biopsy (60). Recently, there is an increase incidence of antimicrobial resistance particularly fluoroquinolone. Data from US SEER–Medicare showed a 2 fold increase in hospitalization rate for infectious complication as compared to controls (7). The risk of sepsis is similar between the first and subsequent biopsies (74). There was an increased incidence of infectious complications following TRUS-Biopsy between 1996 and 2005. There was an increased hospital admission from 1.0% to 4% in this duration and about 70% were related to sepsis (75). There was a significant increase in hospital admission following prostate biopsy during 1993 to 2010. Majority of infection related complications resulted from E coli, with increased resistance to fluoroquinolone, ampicillin and sulfamethoxazole- trimethoprim (76).

Bleeding following Prostate biopsy:

Bleeding following TRUS-Biopsy is one of the most common complication which bothers patient significantly. These include hematuria, hematospermia, and hematochezia or rectal

bleeding. Factors responsible for these complications are size of prostate gland, anticoagulation drugs, and number of biopsy cores.

Hematuria:

Hematuria is common after prostate biopsy, with incidence of 10–84% (71,75,77). This wide range is because of different definitions for hematuria (blood seen in urine, requirement of catheterisation or need for hospitalisation) and duration. One study has reported incidence of hematuria as 65.8% based on questionnaires, in majority of patients it did not bother to them (only about 6% patient considered it as a major problem) (77). Hematuria for >3 days was reported in about 23% of patients. Incidence was more in case of large prostate size (78)(60). Increased risk of bleeding as the number of cores increase during prostate biopsy is controversial. Ghani and colleague performed biopsy in 760 men and found no difference in the prevalence of hematuria and number of biopsy cores (79). Another study showed increased chances of bleeding as the number of biopsy core increased (80). Prostate biopsy needle size does not affect bleeding rates. Hospital admission following prostate biopsy was reported as 1.4% within 30 d, out of which 20% were related to bleeding (75). Gross hematuria requiring catheterization following biopsy was noted in 0.4% of patients, bleeding requiring admission in 0.14% patient (81). Mild hematuria is commonly noticed after biopsy but it is very rare to have significant bleeding which require hospitalisation (<1% incidence) (66).

Hematochezia or Rectal bleeding:

Incidence of hematochezia is ranging from 1.3% and 45% (71). The various studies have reported increasing rate of bleeding with extended prostate biopsy and patients on anticoagulation but it was not related to size of prostate biopsy needle (79,82). In majority of cases, rectal bleeding was common (36.8%), but it was a major problem in only 2.5% cases (77). Patients who are counselled properly regarding rectal bleeding and hematuria, it is of little consequence. It is very rare to notice massive rectal bleeding following prostate biopsy and it could be fatal. There are various treatment alternatives available to control rectal bleeding like balloon tamponade, injection of adrenaline endoscopically, sclerotherapy or endoscopic direct vessel clipping (83–86).

Hemospermia:

Varied incidence of hemospermia reported in literature (1.1–93%) (87). This could be related cultural issues, varied perceptions or social stigma. One study reported almost all patient had hemospermia (92.6%). This is an alarming 25% of men (77). Post prostate biopsy, there was a gradual decline in hemospermia over time. There was an anxiety and decreased sexual activity with hemospermia which improved subsequently. ERSPC study showed hemospermia in about 50% patient and it was found that incidence of hemospermia is related to age, prostate volume, and history of TUR of prostate (78). As the number of biopsy core increases the incidence of hemospermia also increases.

Anticoagulation:

Discontinuation of anticoagulation prior to biopsy is a very critical issue and it has to be looked at thoughtfully. There is cardiovascular risk when anticoagulation is stopped while a bleeding risk and associated complications with continuation of these drugs. There are

factors which modify the balance of risks and benefits. Giannarini and colleague assessed the role of aspirin continuation before prostate biopsy and evaluated 196 men, divided them into three groups, aspirin group, aspirin replaced with LMWH or no aspirin group. All three groups did not show any difference in bleeding rate ($p = 0.26$). However, there was prolonged duration of bleeding for men on anticoagulation. This study showed that aspirin prolongs duration of bleeding but it did not increase bleeding risk (88). It is safe to perform prostate biopsy without discontinuing aspirin as the risk of bleeding is very low; however, same conclusion can be drawn for warfarin and clopidogrel as there are very few studies had looked into it.

Pain after TRUS biopsy of Prostate:

For TRUS biopsy prostate, analgesia was not always routinely used. However, it causes significant pain and discomfort as well as anxiety. Increased pain was reported as reluctance to second biopsy, if required (77).

Measures of pain:

Visual analogue scale (VAS; 0 = none and 10 = worst pain) is the most commonly used measure to assessed pain. Other method is a five-point scale . When using VAS to assess the pain, it is considered clinically meaningful if VAS >2 points.(66)

Pain management related to biopsy of Prostate:

There are numerous factors which can contribute to pain during biopsy; anxiety is the main concern, which may be greater in young patients. Size of the needle does not affect the severity of pain (82). There are other factors affecting pain during biopsy like compliance of

rectum, volume of prostate and biopsy cores (88). Left lateral decubitus position during biopsy was found to have slightly less pain, although it did not reach statistical significance. Sedo analgesia prior to prostate biopsy has been described. Although very effective, it is difficult for use as outpatient, and it also need monitoring of patient post biopsy with significant increase of expenditure. However, it remains a viable option for select patient. Peri prostatic nerve blockade (PPNB) is a safe procedure, and 20 cc of Lignocain significantly reduces pain. Various techniques have been described for PPNB; infiltration to the apex, infiltrating the basal region and combined techniques. One study has assessed peri operative difficulty if any in those patients who received nerve block during biopsy and do not found any significant difference in operability in those in whom PPNB was given (89). Intra rectal creams, gels, and lidocaine suppositories are described to reduce the pain during biopsy. These agents found to be more effective when compared with placebo but most studies found them to be inferior compared to PPNB (90).

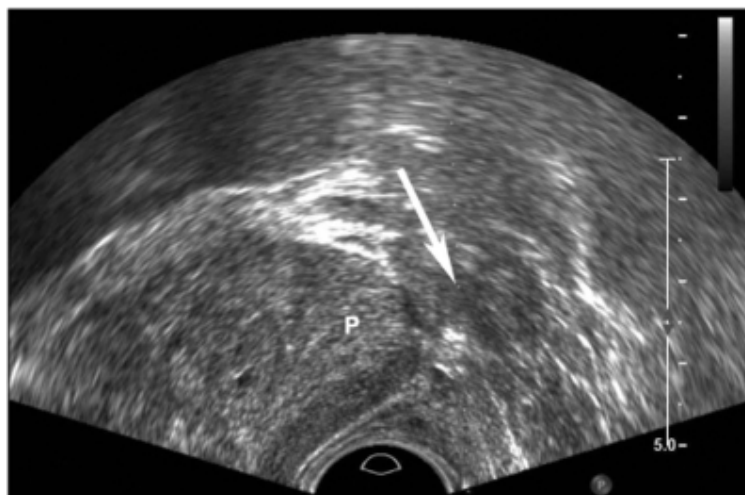


Figure 5: Ultrasound image of the anaesthetic injection site during peri- prostatic nerve bundle block. Arrow indicates the site of lidocaine injection. P; Prostate

LUTS and retention of urine after biopsy:

Risk of urinary retention is very low following prostate biopsy. The incidence reported in literature is 0.2% to 1.7% (60,81,3). Number of cores taken during biopsy has no correlation with incidence of retention of urine (3). Raaijmakers and colleague have noted certain factors which are directly linked to retention of urine, includes volume of prostate, ratio of transition zone to total prostate volume and a higher IPSS score (60,78). Affect of α -blockers on the incidence of urinary retention following prostate biopsy have been studied. 66 patients were randomized to Tamsulosin versus no Tamsulosin in a prospective study. There was an increased flow rate & significant improvement in IPSS noted in the Tamsulosin group. Overall risk of retention is low (<2%). About >25% patients had deterioration of lower urinary tract symptoms after biopsy for a brief period, even though it is not always recommended to use alpha blocker for majority of patients (91).

Mortality following Prostate biopsy:

Overall, there is a very low risk of mortality following prostate biopsy. A Canadian population based study (N=75,190) showed 0.09% mortality following prostate biopsy (75). An analysis of SEER data (N=17,472) suggested mortality rate as 0.31% (7). Hospital admission due to infectious complication following prostate biopsy play a significant role mortality.

Materials and Methods

Design and duration of study:

A prospective observational study design carried out at our institute from September 2013 to March 2014.

Approval of Institutional Review Board and Ethics Committee was obtained. The IRB no.8452

Inclusion Criteria:

- Raised serum prostate specific antigen (PSA >4.0 ng/ml) or
- Abnormal digital rectal examination (DRE) or
- Both
- Outside biopsy report suggestive of prostate cancer but no slides/blocks available for review

Exclusion Criteria:

- Patients refused to give consent
- Patients started on prophylactic antibiotics two days prior to biopsy

All consecutive patients under evaluation of suspected carcinoma prostate were included in the study. All patients underwent detailed history and physical examination. Co-morbidities were assessed if any, especially diabetes mellitus. Detailed medication history including steroid, insulin, anti-coagulation medication, anti platelet drugs was taken. If patient was on Warfarin, it was decided to change to either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) with an appropriate time of bridge therapy before proceeding for prostate biopsy. Similarly, if patient was taking antiplatelet drug like Clopidogrel, it was planned to discontinue for 7 days at least prior to biopsy.

All patients were asked to give urine sample for culture & sensitivity on prior visit. If urine culture was negative, single dose of Inj. Amikacin 15mg/Kg IV was given just before doing biopsy. But if culture was positive, patients received antibiotics for 3days prior to biopsy and were continued for total of 7 days according to sensitivity.

An information sheet was provided to all patients and those who consented to take part, were included in the study.

Peri prostatic nerve block was given to all patients before TRUS guided prostate biopsy. 5ml of Injection Lignocain 2% (v/v) mixed with 5ml of normal saline and injected 5ml each on both sides. 22 gauge 17cm long spinal needle was used for this purpose.

Standard 12- Core prostate biopsy done in each patient and samples were labelled properly according to site and side of the prostate and sent for pathology.

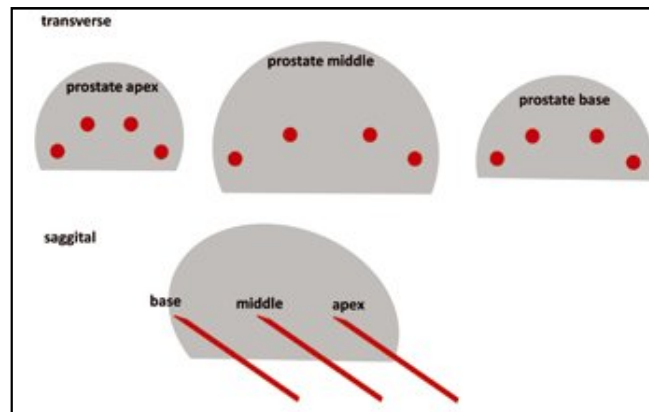


Figure 6: Biopsy locations in a 12-core biopsy

Image courtesy- EAUN prostate biopsy guidelines 2011

Ultrasound machine (B K Medical system) model Flexi focus 200 was utilised for prostate imaging and to guide prostate biopsy. The ultrasound probe (rectal) model 8808e was a 7.5MHz biplane probe with slot for TRUS biopsy needle.



Figure 7: Ultrasonography Machine (Courtesy- B K Medical system) model Flexi focus 200 and Trans rectal probe



Fig 8: 18 Gauge prostate needle biopsy gun. Courtesy- BARD

Outcomes:

Primary outcome was to assess urosepsis requiring hospitalisation.

Secondary outcome was to assess the incidence of other complications following TRUS guided prostate biopsy. These include-

- Fever
- Hematuria
- Hematochezia
- Urinary retention
- Pain or discomfort

All patients' data including follow up, up to 30 days, were prospectively recorded, including duration of hospitalisation including intensive care unit (ICU), if required.

Outcome Definitions:

- Sepsis: SIRS with documented or clinically high suspicion of infection (SIRS includes - temperature $\geq 38\text{ }^{\circ}\text{C}$ or $< 36\text{ }^{\circ}\text{C}$; heart rate > 90 beats/minute; respiratory rate > 20 breaths/minute or respiratory alkalosis; WBC $> 12,000$ or < 4000 or immature forms $> 10\%$ in case of normal range of total WBC) (6)
- Infection – Any fever post biopsy more than $37.5\text{ }^{\circ}\text{C}$
- Gross hematuria – Visible blood in urine
- Hematochezia – Blood noticed in stool
- Urinary retention – Unable to pass urine after biopsy
- Pain or discomfort – Assessed with visual analogue scale

Sample size calculation:

A target sample size of 95 was calculated using a precision of 4% and 90% desired confidence level for the infection related complications. This was carried out assuming an average incidence of infection related complication of up to 6%. This incidence was arrived at after a comprehensive literature review for this statistics.

$$n = \frac{4 \times p \times q}{d^2}$$

$$p = 0.06$$

$$q = 1 - p = 0.94$$

$$d = 0.004$$

Statistical analysis:

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS®) version 18 (IBM Corporation, USA).

Frequencies and percentages are used to represent the categorical variables. eg; age, prostate volume etc.

Descriptive statistics are used to represent continuous variables, eg; mean standard deviation.

Chi square test and Fisher's exact test were used to find the relationship between two variables.

p value < 0.05 was considered as statistically significant.

The results are represented graphically using Bar charts and tables.

Results

A total of 89 patients underwent TRUS guided prostate biopsy for suspected carcinoma prostate on the basis of raised PSA or abnormal rectal examination during study period. Fourteen patients were excluded from the study as they received oral prophylaxis before prostate biopsy regardless of their urine culture report. The remaining seventy five patients were included in the study.

The demographic characteristics of the patients are given in [Table 1](#). The mean age of patients was 60.69 years. Diabetes and hypertension were the most common associated co-morbid illnesses, being seen in over 58% of the patients. Some of these patients had both diabetes mellitus as well as hypertension as co-morbidities.

Table 1 Demographic characteristic (n=75)	
Age (yrs)(SD)	60.69 (9.57)
Prostate size (cc) (SD)	24.07 (13.29)
PSA (ng/ml)	96.75
Co- morbidity	
▪ DM	18
▪ HT	26
▪ CAD	01
▪ COPD	02
▪ Post CVA	02
▪ CKD	01

Clinical Presentation:

Most common presentation of these patients was lower urinary tract symptoms. During evaluation, they were suspected to have prostate cancer either an abnormal rectal finding or raised PSA. At our institution, we do not do screening for prostate cancer. Therefore the number biopsies performed during the study period was quit small as compared to any other studies where they do routine screening for prostate cancer. Some patients have more than one clinical presentations eg; having LUTS and came with a report of raised PSA (done elsewhere). Similarly, bone pain with LUTS was another common presentation. Details of clinical presentation are given in Table 2

Table 2 Presentation	
LUTS	53
On catheter for retention of urine	10
Hematuria	3
Raised PSA (on screening elsewhere)	16
Bone pain	6
Abnormal rectal examination	62

Pathological Features of Prostate Biopsy:

Among all the patients who underwent TRUS guided prostate biopsy, only 38 patients were diagnosed as adenocarcinoma prostate rest of them did not show evidence of malignancy on biopsy tissue. Majority of non-malignant pathology specimen were reported as focal mild inflammation or chronic prostatitis. One patient's biopsy was reported as granulomatous prostatitis suggestive of Tuberculosis. He had other features suggestive of urinary Tuberculosis.

Majority of cases had higher Gleason's score on biopsy. 63% of patients had Gleason's score >7 and peri-neural invasion was seen in more than 81% of patients. [Table 3](#) shows details of pathological features of prostate biopsy.

Table 3 Pathological features of Prostate biopsy	
Adenocarcinoma prostate	39 (52%)
Gleason score	
▪ >7	24 (61%)
▪ 7	
• 3+4=7	7 (18%)
• 4+3=7	6 (15%)
▪ <7	2 (5%)
Peri-neural invasion	31 (81.58%)
Tumor volume (mean)	56.45%
Number of positive cores	10.82

Patients who were diagnosed as adenocarcinoma prostate on TRUS biopsy or presented with bony pain underwent bone scan. Total of 38 patients had undergone bone scan, out of which only seventeen patients did show evidence of osseous metastasis.

Pain during Prostate Biopsy:

Pain during TRUS biopsy prostate was minimal in majority of patients. On visual analogue scale (VAS), it was 2 or less in 84% patients as shown in Table 4

Table 4 Visual analogue scale VAS (n=75)	
2 or less	63 (84%)
more than 2	12 (16%)

Complications following Prostate Biopsy:

Only five patients developed low grade fever after biopsy which subsided with antipyretics. None of them required hospital admission. Out of these 5 patients, two patient's pre biopsy urine culture was positive, two had sterile culture and one had contaminants in urine sample. Those two patients in whom urine samples were positive, they received appropriate duration of antibiotics before and after procedure according to culture sensitivity.

Another 71 years of age gentleman with multiple co-morbidities, developed urosepsis and septic shock after prostate biopsy. His pre-biopsy urine sample grew two organisms for which he was on antibiotics for 3days according to sensitivity pattern. Despite of this,

patient developed features suggestive of sepsis and was hospitalised. The antibiotic was upgraded as the patient's condition deteriorating. He was kept in ICU for 2 days. The urine and blood culture sent before upgrading the antibiotic did not grow any organism. Total duration of hospitalization was 12 days.

Twenty patients noticed mild hematuria post biopsy which settled in one or two days. Only two patients had several episodes of gross hematuria lasted for more than 2 days which ultimately resolved on its own. None of them required catheterization or bladder wash.

Two patients were catheterised after prostate biopsy as they were having overflow incontinence. One patient was catheterised post biopsy due to sepsis. None of the patient developed urinary retention following prostate biopsy.

Six patients noticed blood in stool after biopsy which settled on its own.

Incidence of hematospermia after prostate biopsy was not assessed in this study population. [Table 5](#) summarizes the complications of Prostate biopsy.

Table 5 Complications following prostate biopsy (n= 34)	
Minor Complications	
▪ Low grade fever	5 (6.7%)
▪ Hematuria < 2 days	20 (26.4%)
▪ Hematochezia	6 (8%)
Major Complications	
▪ Sepsis	1 (1.3%)
▪ Hematuria > 2 days	2 (2.7%)
▪ Urinary retention	0

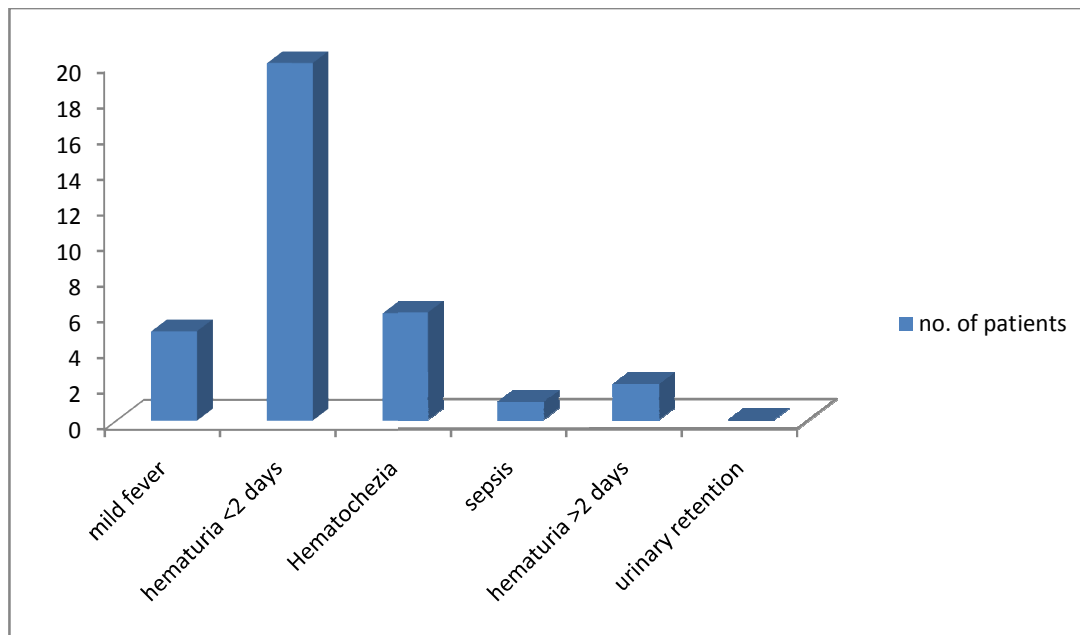


Figure 9: Showing complications following Prostate biopsy

Among all the patients, 20 of them had positive urine culture. Five of them were on per urethral catheter. E. coli was the most common organism found. Most of these urine samples grew single organism. Five urine samples grew 2 organisms and one sample grew three organisms. Most of these multiple organism urine samples were from patients who were on per urethral catheter. Pattern of micro-organisms seen on urine culture samples were shown in [Figure 9](#)

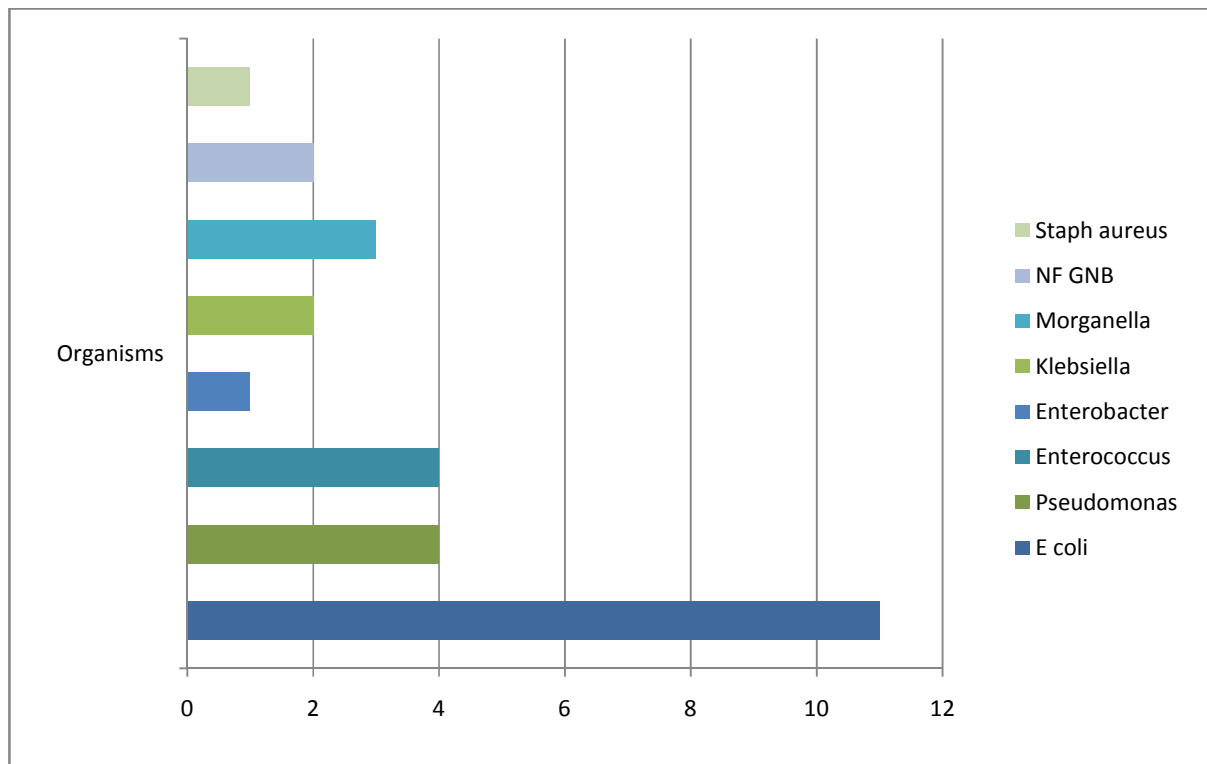


Figure 10: Positive urine culture samples, showing different organisms

Antimicrobial resistance pattern among positive urine culture samples:

There were twenty patients in whom pre-biopsy urine culture was positive. Urinary organisms were found resistant to one or more of the eight most common antimicrobial agents used. Organisms were most frequently resistant to Cefpodoxime in our study. Seven patients' cultures were resistant to Co-trimoxazole and Nitrofurantoin. Only three urine culture samples were resistant to Ciprofloxacin. Reason for apparently low resistance to Ciprofloxacin was because sensitivity for this antimicrobial was not checked in 70% of urine samples. See [figure 10](#) for detail below.

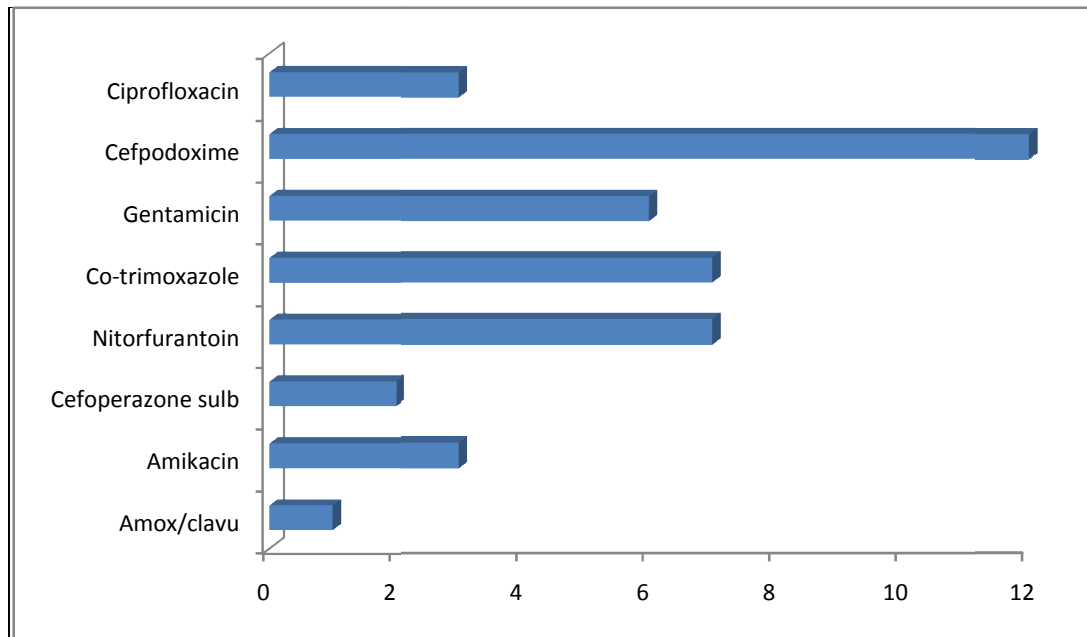


Figure 11: Antimicrobial resistance patterns of pre biopsy urine cultures

Subgroup Analysis:

Relationship of Urine Culture with Infection:

Urine culture	Rate of infection (%)	p Value
Positive	4/20 (20.0%)	0.040
No growth or contaminants	2/55 (3.6%)	

Table 6: Relationship of urine culture with infection

As shown in [Table 6](#), patients with positive urine cultures had more infection as compared to the other group where urine culture was either no growth or contaminants. There was a statistically significant association of positive urine culture with rate of infection.

Relationship of Urine Culture with Hematuria:

Urine Culture	Incidence of hematuria	p Value
Positive	6/20 (30.0%)	0.939
No growth or contaminants	16/55 (29.1%)	

Table 7: Relationship of Urine culture with hematuria

In both groups almost equal number of patients had hematuria. There was no association found between urine culture and incidence of hematuria. See [Table 7](#)

Risk of infection in diabetic patients:

Diabetes mellitus	Incidence of infection (%)	p Value
Present	2/18 (11.1%)	0.626
Absent	4/57 (7.0%)	

Table 8: Risk of infection in diabetics

In our study, it was found that diabetic patients had more incidence of infection compared to non-diabetics. But the association of diabetes and incidence of infection did not reach to a statistical significance as shown in [Table 8](#).

Association of Infection with indwelling urethral catheter:

Per urethral catheter	Rate of Infection (%)	p value
Catheter	0/10 (0%)	1.000
No catheter	6/65 (9.2%)	

Table 9: Risk of infection with indwelling catheter

In our study, ten patients were on catheter prior to prostate biopsy. There was no infection noted in this group following biopsy. Six patients in non catheter group had infection (9.2%). This increase incidence of infection in no catheter group did not reach statistical significance ($p = 1.000$). [Table 9](#)

Discussion

Trans rectal ultrasound guided prostate biopsy has remained the gold standard to diagnose prostate cancer. Biopsy related complications are not uncommon. Majority of the complications are mild and self-limited but sometimes it could be severe and life threatening. Infection and bleeding from urethra and rectum are the most common complications following prostate biopsy. Some recent studies have reported increasing trends of hospitalisation following prostate biopsy due to infection related complications.

To reduce the incidence of infection following biopsy, there were many prophylactic regimens including oral as well as intravenous antibiotics recommended by various studies (56,57). In our study, one dose of intravenous Injection Amikacin 15mg/kg was given just before TRUS biopsy in those in whom urine culture showed no growth or contaminants. Otherwise patients received 3 days of antibiotic course before biopsy and continued for total of seven days according to culture and sensitivity.

Rectal cleansing with povidone-iodine and enema plus antibiotics has been explored by various studies with controversial conclusions. Some studies say that it reduces infectious complications but few of them conclude no difference in complications (58–60). However, Cochrane review has concluded that risk of bacteraemia was reduced with enema plus antibiotics when compared with antibiotics alone but risk of fever or infection was similar in both groups(6). We have not used any kind of rectal cleansing or enema before prostate biopsy.

Loeb S et al have identified various risk factors for infectious complications. These include; Co-morbidities like Diabetes, COPD, Heart valve, benign prostate enlargement , recent urogenital infection, Recent antibiotics, hospitalization, presence of a catheter, positive pre

biopsy urine culture etc. (66) In our study , the risk factors identified were Diabetes mellitus, COPD, per urethral catheter and positive urine cultures.

Prophylactic antibiotic before prostate biopsy is being used by all centres but the particular antibiotic, dose and duration varies widely among centres. However, most studies showed no significant benefit if duration is more than 24hours (67,69,70). At our centre, we utilised single dose of intravenous Injection Amikacin just before biopsy.

Febrile UTI following prostate biopsy is common. Reported incidence rate of infection in different studies is around 3% (73,74). In our study, only one patient had febrile UTI which progressed to sepsis and required hospitalisation despite of being on antibiotics prior to procedure.

Incidence of fever reported in literature is about 3% to 3.5% (78,92). Our study had reported fever in 6% of patient, higher than reported in previous studies.

Hospitalisation rate in our study was 1.3% similar to other studies in which it was 0.6% to 1.7% (60). But other studies have reported incidence of hospitalisation of 3.1% to 3.06% (73) Another study reported increase in hospitalisation rate from 1% to 4.1% from 1996 to 2005 (75)

Hematuria is very common complaint following TRUS biopsy of prostate. Its incidence varies in literature from 10-84% (71,75,77). There are various definitions of hematuria in different studies (visible blood, need for catheterisation or hospitalisation, also duration of hematuria). In a cohort study, incidence of hematuria was reported as 65.8%, but bothersome hematuria was only 6.2% (77). Our study reported hematuria in 26.4% patients. But bothersome hematuria which lasted for more than 2 days was noted in only 2.7% patients. None of these patients required any intervention and it subsided on its own. A

large prospective study on prostate cancer screening had reported prolonged hematuria (>3 days) in 22.6% and it was correlated with prostate volume (78). We could not assess this association in our study population as the number patient in our study was quit small as compared to ERSPC study where approximately 6000 persons participated. There are studies which had evaluated relationship of hematuria with number of biopsy cores, size of the biopsy needle etc. and showed conflicting results. We did not evaluate these factors in present study.

Incidence of hematochezia ranged from 1.3% and 45%. Studies had shown that incidence of bleeding increases with increased number of prostate biopsy cores and anticoagulative drugs (79). Our study did show incidence of rectal bleeding around 8%. A very low incidence rate as compared to previously reported in various studies. This could be due to smaller needle size used for biopsy and proper patient evaluation before biopsy. In most of the cases of rectal bleeding, if patients are counselled properly regarding rectal bleeding and hematuria, it is of little consequence. It is very rare to see massive rectal bleeding and could be fatal. No such massive hematochezia noted in our study. Rectal bleeding was noted in few patients in our study but it was self limiting.

Hemospermia was noted in almost all studies following prostate biopsy. Its incidence varied from as low as 1% to as high as 93% (87). Gradually it declined over several weeks. Studies have reported anxiety and reduced sexual activity associated with hemospermia which resolved after about eight ejaculations. ERSPC study showed hemospermia in 50.4% (78). Our study population included majority of patients above 60 years of age. And almost all of them did not have intercourse for a long time, either because of decreased libido or due to other socio-economic reasons.

TRUS guided prostate biopsy causes significant amount of pain. Therefore some form of analgesia is mandatory now. One study noted that TRUS biopsy prostate was associated with significant pain and discomfort as well as anxiety. This has resulted in reluctance to subsequent biopsy, among those it was required (77). There are other factors affecting pain during biopsy like rectal compliance, volume of prostate and number of prostate biopsy cores. Left lateral decubitus position during biopsy was found to have slightly less pain, although the difference may not be clinically significant. Various types of anaesthesia/analgesia were described for prostate biopsy. Among them, peri prostatic nerve block (PPNB) is safe and effective procedure. We performed prostate biopsy in left lateral decubitus position and injected 2% Lignocain 5ml diluted with 5ml of normal saline as PPNB. It was very effective in reducing pain during biopsy and majority of our patients (84%) did not have clinically significant pain (based on VAS ≤ 2).

Risk of urinary retention following TRUS-Biopsy prostate is very small (0.2% to 1.7%). Number of cores taken during biopsy has no correlation with incidence of retention of urine. One study had assessed factors directly linked to retention of urine, includes volume of prostate, ratio of transition zone to total prostate volume and a higher IPSS score (78,81,3). In our study, no patient had retention following prostate biopsy. There were two patients with overflow incontinence and therefore were catheterised after prostate biopsy.

Overall, the risk of mortality is very low following prostate biopsy. Some studies have reported it less than 1% (7,75). There was no death in our study.

The subgroup analysis of our study showed that patients with positive urine cultures had increased rate of infection compared to other group with sterile urine culture or contaminants. It was statistically significant. Increased rate of infection among culture positive patients is self explanatory. However, all such patients received a course of antibiotics according to culture and sensitivity, started on 3 days prior to biopsy and then continued for 5 -7 days. Observation from this study suggests that it would have been ideal to complete the course of antibiotic and document a sterile urine culture before proceeding for biopsy.

Another important correlation was made between diabetes and incidence of infection. Although it was not statistically significant, but it was noticed that in diabetic patients incidence of infection was higher. It is a well established risk factor for increase incidence of infection after biopsy (74,93,94).

Patients with indwelling urethral catheter prior to biopsy had low incidence of infection when compared with other group who were voiding, although it was not statistically significant in this study. It could be explained as some of the patients who were voiding but had significant post void residue and that could have contributed to increased incidence of infection. Unlike them, patients who were on urethral catheter, had a decompressed system and hence less to develop infection system. However, indwelling catheter itself leads to colonisation of bacteria and that may cause infection following any urological procedure.

Results of various publications on complication of biopsy are shown in Table 10. Caution must be exercised during comparisons with other studies due to differences in population, sample size, biopsy core, and different definitions of complication as well as follow-up. The

incidences of hematuria and hospital admission rates are comparable with published studies. Incidence of fever was higher in our study. Thorsten H. Ecke et al had very low rate of gross hematuria (6.5%). This could be because their definition of gross hematuria was including only those who complained of persistent gross hematuria of more than 2 weeks after biopsy (95).

Table 10 Review of recently published studies									
Investigator	Year	No.	Biopsy cores	Enema	AB	Fever (%)	Hosp (%)	Hemat uria (%)	Retent ion (%)
Djavan	2001	1015	8	NA	Yes	3.0	NA	15.9	2.6
Raaijmakers	2001	5802	6-7	No	Yes	3.5	0.5	22.6	0.4
Thorsten H.	2008	336	12	Yes	Yes	1.8	0.6	6.5	0.3
Present study	2014	75	12	No	Yes	6.7	1.3	26.4	0

AB = antibiotics; hosp = hospitalization; NA = not available

Conclusion

Trans rectal ultrasound guided prostate needle biopsy is safe for diagnosing prostate cancer.

The most common complication was hematuria in 26.4% of cases, followed by low grade fever. Incidence of sepsis requiring hospitalisation was very low in our study. Increased incidence of infection in patients with positive urine culture suggests that treatment of infection and documentation of negative urine culture before biopsy may be wiser. Positive 7pre-biopsy urine culture and diabetes mellitus are risk factors which should be looked into before planning prostate biopsy.

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Annexure

PATIENT PROFORMA

To Evaluate the Complications of TRUS guided Prostate Biopsy

Study number: _____

Patient name:

Hospital no:

Age:

Address:

Presenting complaint: LUTS

O/E: Abnormal DRE -

Raised PSA

Miscellaneous

Uroflow-PVR:

PSA level: 1) [T] [F]

Urine C/S:

Urine microscopy:

If culture positive, which antibiotic and duration?

Symptoms of UTI:

Antibiotics used:

If yes, which antibiotic?

Is patient on catheter?

Co-morbid illness:

Diabetes

Hypertension

Coronary artery disease

Medication use:

Steroid use

DM: OHA

Insulin

Anticoagulation:

Aspirin -

Clopidogrel -

Warfarin -

Bone scan: Done/not done

Metastatic/Non metastatic

TRUS volume of prostate:

Biopsy features:

No. of cores -

No of positive cores –

Gleason score –

Tumor volume –

Perineural invasion -

Lymphovascular invasion -

Misc. –

Pain score – VAS (Visual analogue scale):

0 ————— 10

0 No pain

10 Intolerable pain

Complications:

- Infection including sepsis
- Gross hematuria
- Bleeding per rectum
- Hematospermia
- Acute urinary retention
- Hospital admission

Hospital admission –

No. of days –

Need for ICU care - Yes No

Blood culture-

Urine culture-

Antibiotics

Christian Medical College, Vellore

Department of Urology

To Evaluate the complications of TRUS guided prostate biopsy

Information sheet

You are being requested to participate in a study to evaluate the complications of TRUS biopsy of prostate.

You are suspected to have prostate cancer. And planned to undergo ultrasound guided prostate biopsy. The procedure will be done under local anaesthesia. Under ultrasound guidance, prostate biopsy will be done through anal passage.

The procedure has certain risks. These include blood in urine, urinary infection, blood in stool, unable to pass urine and very uncommonly, severe infection .

If you take part what will you have to do?

If you agree to participate in this study, you will undergo prostate biopsy after giving antibiotics (Inj. Amikacin 15mg/kg IV single dose) or culture specific antibiotic course for 3days if urine culture is positive. You will be interviewed at the next visit to outpatient (about a week) regarding procedure related complications.

All other treatments that you are already on, will be continued except Warfarin or Clopidrogel. Clopidrogel to be discontinued for min. of 7days and Warfarin to be changed to heparin or other appropriate drug.

If at any time you experience any problems, you will be expected to report this to the doctor.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way

What will happen if you develop any study related injury?

This is an observational study therefore we do not expect any injury to happen apart from prostate biopsy related complications. But if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr. Feroz Mohd Khan (Tel: 0416 2282455/ 2282011).

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: To Evaluate the complications of TRUS guided prostate biopsy

Study Number:

Participant's name:

Date of Birth / Age (in years):

I _____

_____, son/daughter of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. []

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights []

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive any other financial compensation []

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access []

I understand that my identity will not be revealed in any information released to third parties or published []

I voluntarily agree to take part in this study []

Name:

Signature: OR Left Thumb Impression:

Date:

Name & Signature of Principal Investigator/Co-investigator: